DOCKET NO.: 03-02US
Application No.: 10/787,385
Office Action Mailed: 07/31/06

REMARKS

With entry of this amendment, claims 1-31 are pending in the application. No amendments are presented with this response.

Patentability Under 35 U.S.C. § 102

Applicant notes for the record that the Office has substantively reviewed the application and pending claims and has not levied any rejection of claims under 35 U.S.C. § 102. On this basis Applicant understands the Office has fully considered the pending claims and determined that the subject matter therein is novel over all publications and patents of record in the application.

Patentability Under 35 U.S.C. § 103

Applicant notes for the record that the Office has withdrawn the prior rejection of claims 1-23 under 35 U.S.C. § 103, as allegedly unpatentable over Wenig (U.S. Patent No. 4,724,231); Slot, et al. (*Gastroenterology 113*:430-433, 1997); and Garcia-Arieta, et al. (*Biol. Pharm. Bull. 24*:1411-1416, 2001).

Applicant also notes for the record that the Office has withdrawn the prior rejection of claims 24-30 under 35 U.S.C. § 103 as allegedly unpatentable over Wenig (U.S. Patent No. 4,724,231); Slot, et al. (*Gastroenterology 113*:430-433, 1997); and Garcia-Arieta, et al. (*Biol. Pharm. Bull. 24*:1411-1416, 2001).

In view of the foregoing, Applicant understands the Office has fully considered the pending claims and determined that the subject matter therein is nonobvious over all publications and patents of record in the application.

Patentability Under 35 U.S.C. § 112

The Office has maintained the rejection of claims 1, 23, 24, 30 and 31 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, levied in the previous Office Action (Paper No./Mail Date 03142005), for reasons of record and as set forth in the current Office Action (at pp. 2-4).

The central factual basis for the enablement rejection asserted by the Office is that the disclosure allegedly lacks "sufficient AUC data" to support the instantly-pending claims directed to cyanocobalamin formulations and methods providing "a bioavailability of cyanocobalamin when administered nasally of at least about 7% relative to an intramuscular injection of cyanocobalamin."

Applicant respectfully traverses the foregoing grounds for rejection and submit that the instant disclosure fully enables the subject matter set forth in the pending claims.

The Office has not challenged the fact that Applicant's disclosure provides literal, descriptive support for the subject expression pertaining to relative bioavailability. In this regard, the specification clearly teaches that the claimed cyanocobalamin solutions, when administered intranasally, achieve "bioavailability of at least 7% of the bioavailability of an intramuscular (IM) injection of cyanocobalamin." (see, e.g., page 3, lines 22-24). The disclosure further teaches that, in certain embodiments, the minimum bioavailability provided by the claimed intranasal (IN) formulations and methods, compared to bioavailability achieved by IM formulations and methods, is "at least 8%, more preferably at least about 9, 10, 11, or 12%" (see, e.g., page 3, lines 26-28).

These positive assertions regarding enablement rendered in Applicant's disclosure are entitled to a presumption of correctness. As explained in the PTO's Enablement Guidelines, (see, e.g. Example 5E: "Peptides for Treating Obesity," at page 46):

> The Office must accept as being true the statements supporting enablement unless there is an objective reason, usually supported with documentary evidence, to question them.

The Office therefore bears the initial burden to provide factual evidence that is "inconsistent" with an Applicant's assertions regarding enablement. *In re Marzocchi, et al.*, 169 U.S.P.Q. 367 (C.C.P.A. 1971).

Applicant respectfully submits that no such factual evidence has been provided in the record of this application.

The Office sets forth the following assertions in support of the current enablement rejection (at pp. 2-4, underscores added).

> The claims are directed to a solution that, when administered intranasally, have (sic) a bioavailability of at least 7% relative to an intramuscular injection. An adequate representation regarding the bioavailability claimed would be one that provides all of the data necessary to calculate the bioavailability claimed relative to that of an intramuscular injection.
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> Additionally, there are several methods of assessing bioavailability in humans and other animals. The selection of methods depends on the nature of the drug product and makes use of such parameters as

> time of peak plasma concentration, peak plasma concentration and the area under the plasma-time cure(sic) (AUC). However, Applicant does not provide any AUC data for bioavailability of cyanocobalamin delivered via intramuscular injection.
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> Further, Applicant discloses several examples in the specification to demonstrate the relative bioavailability relating to the compositions and methods claims. However, in order to demonstrate relative bioavailability, Applicant must provide four variables for the bioavailability equation. Applicant's disclosure fails to demonstrate relative bioavailability in its examples and does not disclose any AUC data for either route of administration.

The foregoing arguments and technical points fail to demonstrate that Applicant's disclosure is non-enabling for cyanocobalamin formulations having at least about 7% bioavailability upon IN administration relative to IM-administered cyanocobalamin.

Despite that explicit AUC values may not be expressed in Applicant's disclosure for IM-treated subjects, the specification nonetheless fully describes and enables these results. In particular, the data provided in the working examples of Applicant's disclosure encompass all essential data necessary to determine relative AUC values.

Persons of ordinary skill in the art would look first to the literal support provided in the specification (as noted above), which expressly supports the relative bioavailability characteristics of the claimed invention. Next they would look to the data provided in the working examples, from which the artisan would immediately discern that the data fully and directly support these relative bioavailability characteristics.

In this regard, Example I of Applicant's disclosure provides detailed, comparative bioavailability studies between IN and IM cyanocobalamin formulations and methods, the results of which studies are presented at pp. 12-18 of the specification. At page 17, under the heading "PHARMACOKINETIC RESULTS", the following data and conclusions are presented:

> The relative bioavailability for the two IN formulations was 0.9715. Bioavailability when comparing treatment A (Spray) versus treatment C (IM) was 0.6105, and 0.6284 when comparing Treatment B (gel) versus Treatment C (IM).

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> The pharmacokinetic profiles of the spray formulation and the gel formulation are similar for Cmax (1480 pg/mL, 1670 pg/mL, respectively) and AUC_{0-t} (9200 pg*hr/mL, 9700 pg*hr/mL, respectively). Additionally, the median difference for Tmax between the spray and gel IN formulation was less than 15 minutes (-0.24). The C_{max} value for the IM formulation was significantly higher than the C_{max} values for the two IN formulations ($p<0.0001$).

These data are fully determinative of the claimed, relative bioavailability characteristics of Applicant's cyanocobalamin formulations and methods. The absence of comparative AUC values for IM bioavailability does not indicate a literal or technical deficiency of the disclosure in this regard. On the contrary, AUC values for both IN and IM formulations and methods are readily and accurately discerned from the data presented in the application.

To assist the Office in further considering the enablement issues in this case, Applicant submits herewith the Declaration of co-inventor, Anthony Sileno, M.S. As described in ¶ 1 of his Declaration, Mr. Sileno is an artisan currently practicing in the fields of "pre-clinical and clinical development", "screening drug formulations for pharmacokinetic and pharmacodynamic evaluation", and design and implementation of "pre-clinical and clinical Phase I-III studies." It is therefore respectfully submitted that Mr. Sileno is competent to render factual findings and opinion regarding the ordinary state of knowledge, level of skill, and understanding in these arts, and concerning the expectations and perceptions that persons of ordinary skill in these arts would have in evaluating the facts and issues presented in this case.

Consistent with Applicant's position as set forth above, Mr. Sileno presents the following testimony in his Declaration (at ¶ 7, underscores added):

> Even though explicit AUC values are not provided in the instant specification for bioavailability of cyanocobalamin delivered via intramuscular injection, these data are directly derivable from comparative data presented in the application--which data fully support the subject term "a bioavailability of cyanocobalamin, when administered nasally, of at least about 7% relative to an intramuscular injection of cyanocobalamin".

Mr. Sileno further confirms that literal support for the relative bioavailability characteristics of Applicant's IN cyanocobalamin formulations and methods is found throughout the specification (Sileno Declaration ¶ 8).

In ¶ 9 of his Declaration, Mr. Sileno attests that the relative bioavailability characteristics of the claimed, IN cyanocobalamin solutions represent:

> a standard pharmacokinetic description, such as is commonly used and widely understood in the art" (see, e.g., specification at page 6, line 22 to page 7, line 13). Consistent with this common usage, the specification provides explicit methodology and results, in the form of detailed comparative bioavailability studies and data presented in the Examples, which demonstrate the relative bioavailability characteristics of the claimed solutions. The data from these examples clearly and comprehensively support this relative bioavailability characteristic in a manner that would be readily understood and practiced by persons of ordinary skill in the art.

To support these conclusions, Mr. Sileno cites to specific passages of the specification (page 17, under the heading "PHARMACOKINETIC RESULTS"), where he notes the following description is provided (Sileno Declaration at ¶ 10):

> The relative bioavailability for the two IN formulations was 0.9715. Bioavailability when comparing treatment A (Spray) versus treatment C (IM) was 0.6105, and 0.6284 when comparing Treatment B (gel) versus Treatment C (IM).
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> The pharmacokinetic profiles of the spray formulation and the gel formulation are similar for C_{max} (1480 pg/mL, 1670 pg/mL, respectively) and AUC_{0-t} (9200 pg*hr/mL, 9700 pg*hr/mL, respectively). Additionally, the median difference for Tmax between the spray and gel IN formulation was less than 15 minutes (-0.24). The C_{max} value for the IM formulation was significantly higher than the C_{max} values for the two IN formulations ($p<0.0001$).
>
> Relative Bioavailability was assessed by examining the ratio of the nasal B12 spray group mean to the reference group mean with regard to AUC. The ratio is derived by dividing the AUC IN by the AUC IM, therefore, the IM AUC is used in the equation to calculate relative bioavailability, even if it's not presented in the application.

> The ratio of the AUC is an appropriate way to represent bioavailability, for example 12% bioavailability is just a 0.12 ratio of the AUC and multiplied by 100 is 12%.

Based on these teachings from the specification, Mr. Sileno presents further testimony (at ¶ 11), as follows:

> Even though these data do not expressly provide comparative AUC values for IM bioavailability of cyanocobalamin from the described studies, these values are readily and accurately derivable from the data that are presented. Persons of ordinary skill in the art would readily discern this aspect of the description, and no experimentation beyond the results provided in the disclosure would be necessary to determine the subject, relative AUC values.

Mr. Sileno next presents express, factual support for the foregoing conclusions, which again is based directly on the teachings of Applicant's specification. In particular, at ¶¶ 12-14 of his Declaration, Mr. Sileno attests that:

> The comparative bioavailability study results cited from the specification above, demonstrate that the "relative bioavailability" ratio of the spray versus IM, and gel versus IM, is 0.6105, and 0.6284, respectively. As the disclosure clearly indicates, these ratios were obtained by dividing the AUC of the spray, or gel, by the AUC of IM-administered cyanocobalamin. Therefore, the AUC for the IM is readily discerned based on the ratios 0.6105 and 0.6284—a simple mathematical calculation from the AUC of spray and gel and the AUC for the IM is obtained as 15000 pg*hr/ml. As the specification also clearly indicates, these data were dosed normalized according to conventional practice (to the appropriate dose multiple based on a dose of 500 µg given intranasal and 100 µg given by IM; see, e.g., pages 12-16).
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> The skilled artisan would have readily understood these data and fully appreciated that the dose normalized data fully evinced a ratio of bioavailability between the IN cyanocobalamin solutions of the invention and IM-administered cyanocobalamin—which ratio as exemplified in the disclosure is shown to correspond reasonably to the claimed value of "at least about 7%". This determination requires nothing more than a standard mathematical operation to derive the dose normalized relative AUC values for the IN spray and IM injection. In the example provided on page 17, this standard operation/result is 0.6105 X 100 µg/500µg X100 = 12%; or a ratio of the AUC between the IN spray and IM injection of 0.12. In addition to these clearly founded values, the

> actual arithmetic AUC are provided on page 17 of the specification for the spray and gel as 92000 and 97000 pg*hr/mL, respectively. These data, cross referenced to the corresponding data for IM-administration, likewise fully evince the corresponding AUC for the IM injected study comparator.
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> As such, the arithmetic mean of the AUC for IM is readily calculated as 15000 pg*hr/mL (derived quite simply by reverse mathematical operation from the ratios given--for example for the spray 92000/AUC IM = 0.61 ratio). When dose normalized according to the disclosure, these data correspond directly to an exemplary relative bioavailability value within the described ranges set forth in the specification (e.g., as described at page 8, lines 32-35-- "wherein the solution of cyanocobalamin has a bioavailability of at least 7%, more preferably at least about 8, 9, 10, 11, 12% or more of the bioavailability of an intramuscular injection of cyanocobalamin.")

On the basis of these facts, Mr. Sileno concludes that "the data provided in the instant specification fully support the subject matter pertaining to relative bioavailability recited in the pending claims." (Sileno Declaration at ¶ 15.) Consistent with this interpretation, Mr. Sileno further attests that:

> The disclosure in this context is fully correlated and commensurate with the language and scope of the claims--such that skilled artisans in this field would accept the representations and data set forth in the disclosure as sufficient to satisfy the requirements articulated by the Examiner (i.e., to "enable cyanocobalamin compositions and methods of using the composition, wherein the claimed compositions yield "a bioavailability of about 7% relative to an intramuscular injection of cyanocobalamin" (Office Action at p. 3). Indeed, the data provided in the specification directly evince that the formulations and methods claimed yield a bioavailability of cyanocobalamin, when administered nasally, of at least 7% relative to an intramuscular injection of cyanocobalamin. Skilled artisans would have been readily able to practice this aspect of the invention of claims 1-31, which I would regard as a routine undertaking in assessing pharmacokinetics and pharmacodynamics of the currently claimed formulations and methods. The instant disclosure fully conveys this subject matter in conventional terms. Implementation, practice, and validation of this aspect of the invention would not require undue experimentation, but is in fact directly demonstrated by the data and description provided in the application. (id., underscore added)

The findings and conclusions presented in Mr. Sileno's Declaration strongly support Applicant's position--that their disclosure provides all essential data necessary to determine relative AUC values, for both IN- and IM-administered cyanocobalamin, and that the disclosure fully demonstrates that Applicant's formulations and methods achieve "bioavailability of at least 7% of the bioavailability of an intramuscular (IM) injection of cyanocobalamin."

In addition to the foregoing facts and authority, Mr. Sileno provides additional evidence relating to enablement, by reference to a Phase I Pharmacokinetic Study that he designed, directed, monitored, and reviewed for an IN cyanocobalamin formulation according to the pending claims (Sileno Declaration at ¶¶ 16-20; Phase I Pharmacokinetic Study Report, Appendix B). Mr. Sileno also participated in submission and review of these Study results before the FDA.

As noted in ¶ 16 of Mr. Sileno's Declaration, the FDA specifically reviewed and considered relative bioavailability data and findings between intranasal and intramuscular cyanocobalamin formulations and methods, "as a key aspect of this Report."

> The FDA accepted these relative bioavailability data and findings, and ultimately approved Nastech's New Drug Application (NDA) for an intranasal cyanocobalamin solution (currently marketed as Nascobal®, a widely prescribed treatment for Vitamin B_{12} deficiency). The relative bioavailability characteristics of the approved Nascobal® product compared to IM cyanocobalamin formulations and methods, are fully supported by the '385 specification, and accurately recited in the currently pending claims. (id., underscore added)

Considering the similar focus and positive outcome of the FDA's review of Nascobal® to the instant enablement issues, it is most significant that the relative bioavailability methods and results described in the '385 specification "were taken directly taken from the Phase I Pharmacokinetic Study" (Sileno Declaration, at ¶ 18; comparing pages 12-18 of specification, to pages 27-42 of the Phase I Pharmacokinetic Study Report, Appendix B).

Mr. Sileno closes his Declaration with the following findings and conclusions ¶¶ 19-20):

> There are no substantive/technical deficiencies in the relative bioavailability methods and results described in the '385,

compared to the corresponding bioavailability methods and results presented in the Phase I Pharmacokinetic Study Report.

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Although AUC values are expressed for IN- and IM-treated subjects in the Phase I Pharmacokinetic Study Report, the expression of these values provides no additional substantive information in comparison to the data and results provided in the '385 specification. On the contrary, all essential information to determine IN versus IM AUC values found in the Phase I Pharmacokinetic Study Report were incorporated directly into the '385 specification. Persons of ordinary skill in the art, examining the pharmacokinetic data presented in the '385 specification, would immediately be apprised of the "relative bioavailability" characteristics of the claimed formulations and methods.

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[P]ersons of ordinary skill in the art could immediately determine AUC values for both IN- and IM-treated subjects based on the data provided in the '385 specification. This determination, based on a simple mathematical operation as described above, would require no additional information, nor experimentation. In other words, the data and conclusions provided in the '385 specification are for all purposes *equivalent* to the data and conclusions provided in the Phase I Pharmacokinetic Study Report--which the FDA expressly relied upon to conclude that Nascobal® achieves high, therapeutically effective, relative bioavailability compared to IM cyanocobalamin formulations and methods, consistent with the relative bioavailability terms presented in the instant disclosure and recited in the pending claims.

In view of the evidence and authority presented above, Applicant respectfully submits that its disclosure fully supports the pending claims. In this regard, the disclosure is "reasonably correlated" with the scope of the claims, such that skilled artisans would have been able to practice the invention commensurate with the claims, without "undue experimentation." Accordingly, the rejection of claims 3, 14, 20, 31 and 37 under 35 U.S.C. § 112 is respectfully submitted to be overcome.

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CONCLUSION

The present Amendment is in response to the Office Action dated July 31, 2006. It is believed that no fee is required for this submission. Should, however, the U.S. Patent and Trademark Office determine that any fee is due or that a refund is owed for this application, the Commissioner is hereby authorized and requested to charge the required fee and/or credit the refund owed to our Deposit Account No. 502769.

Applicant believes that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at (425) 908-3643.

Respectfully Submitted,

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